

Incidence, survival, and treatment of localized and metastatic neuroblastoma in Germany 1979-2015

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Supplemental Table S1 Treatment schemes for patients with localized neuroblastoma (stages 1-3 according to Evans et al. for NB 79-NB85 [9] and according to INSS [6] for NB90-NB2004)

Trial	Surgery	Chemotherapy	Radiotherapy
NB 79	1,2,3: at diagnosis	1,2: none 3: 3 cycle ACVD or 5 cycles AC	II: local III: progressing tumors
NB 82	1,2,3: at diagnosis	1: none 2: w/o regional lymph nodes: none; with regional lymph nodes: 3 cycles AC	I: none II: none
NB 85	3: 2nd look after chemotherapy 1,2,3: at diagnosis	3: 2 cycles ACVD and 2 cycles PCVm 1: none 2: w/o regional lymph nodes: none; with regional lymph nodes: 3 cycles AC	3: 30 Gy at residual tumor
NB 90	3: 2nd look after chemotherapy (± radiotherapy) 1,2,3: at diagnosis 2,3: 2nd look after chemotherapy	3: 2 cycles ACVD + 2 cycles PCVm, poor response: + 3 cycles Ivp 1: none 2,3A/B: 2 cycles N1 and 2 cycles N2 3C/D: 4 cycles N1 and 4 cycles N2, or 6 cycles D1 and 6 cycles D2 (1y)	III: 24-30 Gy at residual tumor 3C/D: 24 Gy ≤3 y., 30 Gy >3 y. at tumor bed
NB 97	<1y 1,2,3 and >1y 1,2 resectable: at diagnosis ± 2nd look after 6-12 months <1y 1,2,3 with symptoms, 3: at diagnosis biopsy or removal, 2nd look after chemotherapy	none none	none none
NB2004	1,2,3 observation group: at diagnosis, residuals after 1-2 years: 2nd look 2,3,4 medium risk group: at diagnosis, 2nd look after chemotherapy	2 unresectable, 3: 2 cycles N5 and 2 cycles N6 1,2,3, with threatening symptoms or localized progression: N4 cycles (2-4) until stable 2,3,4 medium risk group: 3 cycles N5, or 3 cycles N6, or 4 cycles N7, or 9 cycles RA	none 36-40 Gy at primary tumor (mIBG uptake after chemotherapy)

Supplemental Table S2 Chemotherapy cycles as used in the German trials NB79-NB2004

Designation	Trial	Number of cycles		Drugs
		HR	Non-HR	
ACVD	NB79	3	3	Doxorubicine 35 mg/m ² d d1 push i.v.
	NB82	5	2	Cyclophosphamide 150 mg/m ² d d1-7 1h i.v.
	NB85	3		Vincristine 2.0 mg/m ² d d8 push i.v. Dacarbazine 250 mg/m ² d d1-4 1h i.v.
AC	NB79	5	5	Doxorubicine 35 mg/m ² d d1 push i.v.
	NB82		4	Cyclophosphamide 150 mg/m ² d d1-7 1h i.v.
ASCT	NB85	1		Total body irradiation 2x2 Gy/d d -4 to -2 (12 Gy) Melphalan: 180 mg/m ² d d -1 push i.v.
	NB90	1		Melphalan 30 mg/m ² d d -8 to -5 push i.v. Etoposide 50 mg/kgxd d -4 4h i.v.
	NB97/2004	1		Carboplatinum 500 mg/m ² d d -4 to -2 1h i.v. Melphalan 45 mg/m ² d d -8 to -5 push i.v. Etoposide 40 mg/kgxd d -4 4h i.v. Carboplatinum 500 mg/m ² d d -4 to -2 1h i.v.
C	NB82		3	Cyclophosphamide 5 mg/kgxd d1-5 1h i.v. or p.o.
	NB85		3	
D1	NB90	6	6	Melphalan 8 mg/m ² d d1-5 oral Etoposide 100 mg/m ² d d1-5 oral
D2	NB90	6	6	Vincristine 1.5 mg/m ² d d1 Cyclophosphamide 150 mg/m ² d d1-7 p.o.
IVp	NB85	3		Ifosfamide 4 g/m ² d d1, 3 g/m ² d d2-3 72h cont. i.v. Etoposide 125 mg/m ² d d4-5 1h i.v.
N1	NB90	4	2	Cisplatinum 40 mg/m ² d d1-4 (96h cont. i.v.) Etoposide 100 mg/m ² d d1-4 (96h cont. i.v.) Vindesine 3 mg/m ² d d1 1h i.v.

Designation	Trial	Number of cycles		Drugs
		HR	Non-HR	
N2	N90	4	2	Vincristine 1.5 mg/m ² d d 1 and 8, 1h i.v. Dacarbazine 200 mg/m ² d d1-5 1h i.v. Ifosfamide 1.5 g/m ² d d1-5 120h cont. i.v. Doxorubicine 30 mg/m ² d d6-7 48h cont. i.v.
N3	NB90		1-2	Doxorubicine 0.5 mg/kgxd d1,8,15,22 push i.v. Vincristine 25 µg/kgxd d1,8,15,22 push i.v.
N4	NB97	<6 m of age	1-4	Doxorubicine 0.5 mg/kgxd d1,3,5 0.5h i.v. Vincristine 25 µg/kgxd d1,3,5 push i.v. Cyclophosphamide 10 mg/kgxd d1-7 p.o.
N5	NB97	3	2	Cisplatinum 40 mg/m ² d d1-4 96h cont. i.v. Etoposide 100 mg/m ² d d1-4 96h cont. i.v. Vindesine 3 mg/m ² d d1 1h i.v.
N6	NB97	3	2	Vincristine 1.5 mg/m ² d d 1 and 8, 1h i.v. Dacarbazine 200 mg/m ² d d1-5 1h i.v. Ifosfamide 1.5 g/m ² d d1-5 120h cont. i.v. Doxorubicine 30 mg/m ² d d6-7 4h i.v.
N7	NB97		4	Cyclophosphamide 10 mg/kgxd d1-8 p.o.
N8	NB2004		2	Topotecan 1.0 mg/m ² d d1-7 168h cont. i.v. Cyclophosphamide 100 mg/m ² d d1-7 1h i.v. Etoposide 100 mg/m ² d d8-10 1h i.v.
PCVm	NB82	5	2	Cisplatinum 20 mg/m ² d d1-5 1h i.v. (mod. July 87: 40 mg/m ² d d1-5)
	NB85	3	2	Cyclophosphamide 200 mg/m ² d d1-5 1h i.v. (omitted July 87) Vepeside 100 mg/m ² d d5 1h i.v. (mod. July 87: 100 mg/m ² d d1-5)
RA	NB97	9		Isotretinoin 160 mg/m ² d d1-14, then 14 days break (months 1-6 and 10-12) (substituting αGD2 antibody therapy during 2002-2004)
	NB2004	9		Isotretinoin 160 mg/m ² d d1-14, then 14 days break (months 1-6 and 10-12)

Supplemental Table S3 Treatment schemes for patients with stage 4S neuroblastoma (according for NB 79-NB85 to Evans et al. [9] and for NB 90-NB2204 according to INSS [6])

Trial	Surgery	Chemotherapy	Irradiation
NB 79	No recommendation	No recommendation	No recommendation
NB 82	Biopsy at diagnosis >1year of age: removal of residuals	< 6 months: wait and see Large liver and poor irradiation effect: 3 cycles C (i.v.) > 6 months: 4 cycles ACVD (50% dose)	Large liver: 4.5 (1st choice)
NB 85	Biopsy at diagnosis 2nd surgery 2y after dx	Large liver and poor irradiation effect: 3 cycles C (p.o.)	Large liver: 4.5 – 12 Gy (1st choice)
NB 90	Biopsy at diagnosis 2nd surgery 8 months after dx	Not critically ill: none Critically ill: 1-2 cycles N3	Poor chemotherapy effect: 7.5-12 Gy
NB 97/2004	Biopsy at diagnosis 2nd surgery 6-12 months after dx	No threatening symptoms: none Threatening symptoms: N4 until stop of progression	None

Supplemental Table S4 Additional treatment elements in HR neuroblastoma

Name	Trial	Randomization	Dosage
α GD2 antibody	NB97	No	ch14.18 BioInvent 20 mg/m ² d d1-5 8h i.v., 6 cycles, 1 year (1997-2002)
Interferon β	NB79	Yes	2x10 ⁶ U/m ² d daily d1-21, 3x/week d 22-230
mIBG therapy	NB85	No	100-125 mCi per application, maximal 3 times in patients with mIBG uptake after 6 cycles chemotherapy
	NB90	No	100-300 mCi in patients with mIBG uptake before ASCT
	NB97	No	100-300 mCi in patients with mIBG uptake before ASCT
Radiotherapy	NB85	No	Unresectable primary tumor after chemotherapy: 24 Gy (\leq 3y) and 30 Gy ($>$ 3y) Symptomatic metastases after chemotherapy: 24 Gy (\leq 3y) and 30 Gy ($>$ 3y) TBI for ASCT: 12 Gy
	NB90	No	Primary tumor: 24 Gy (\leq 3y) and 30 Gy ($>$ 3y) Bone metastases (maximal 4): 24 Gy (\leq 3y) and 30 Gy ($>$ 3y)
	NB97	No	Primary tumor mIBG uptake after chemotherapy: 36-40 Gy
	NB2004	No	Primary tumor mIBG uptake after chemotherapy: 36-40 Gy

Supplemental Table S5 Standard induction and myeloablative chemotherapy 2017 for high-risk neuroblastoma

Childrens Oncology Group (US) [8]

Induction chemotherapy

Cycle 1 and 2

Cyclophosphamide	400 mg/m ² d,	d1-5,	30 minutes i.v.
Topotecan	1.2 mg/m ² d,	d1-5,	30 minutes i.v.

Cycle 3 and 5

Cisplatin	50 mg/m ² d,	d1-4,	1 hour i.v.
Etoposide	200 mg/m ² d,	d1-3,	2 hours i.v.

Cycle 4 and 6

Cyclophosphamide	2.1 g/m ² d,	d1-2,	6 hours i.v. (+ Mesna 420 mg/m ² d)
Doxorubicine	25 mg/m ² d	d1-3,	72 hours continuous infusion
Vincristine	0.67 mg/m ² d	d1-3,	72 hours continuous infusion

Myeloablative chemotherapy (tandem)

1st myeloablative cycle

Cyclophosphamide	500 mg/m ² per dose every 8 hours	1 hour i.v. up to a total of 12 doses	
		d -5 to -2	
Thiotepa	900 mg/m ² d	d -7 to -5	2 hours i.v.

2nd myeloablative cycle

Carboplatin	375 mg/m ² d	d -8 to -5	96 hours continuous infusion
Etoposide	300 mg/m ² d	d -8 to -5	96 hours continuous infusion
Melphalan	60 mg/m ² d	3 days	

German Pediatric Oncology

Cycle 1,3,5

Cisplatin	40 mg/m ² d	d1-4	96 hours cont. i.v.
Etoposide	100 mg/m ² d	d1-4	96 hours cont. i.v.
Vindesine	3 mg/m ² d	d1	1 hour i.v.

Cycle 2,4,6

Vincristine	1.5 mg/m ² d	d1, 8	1 hour i.v.
dacarbazine	200 mg/m ² d	d1-5	1 hour i.v.
ifosfamide	1.5 g/m ² d	d1-5	120 hours cont. i.v (+Mesna 900 mg/m ² d)
doxorubicine	30 mg/m ² d	d6-7	4 hours i.v

Myeloablative chemotherapy

Melphalan	45 mg/m ² xd	d -8 to -5	30 minutes i.v.
Etoposide	40 mg/kgxd	d -4	4 hours i.v.
Carboplatin	500 mg/m ² xd	d -4 to -2	1 hours i.v.

Japan Children's Cancer Group [10]***Induction chemotherapy***Cycle 1

Cyclophosphamide	1.2 g/m ² d,	d1	1 hour i.v.
Vincristine	1.5 mg/m ² d	d1	bolus i.v.
Pirarubicine	40 mg/m ² d	d3	1 hour or bolus i.v.
Cisplatin	20 mg/m ² d	d1-5	120 hours cont. i.v.

Cycle 2,3,4,5

Cyclophosphamide	1.2 g/m ² d,	d1-2	1 hour i.v.
Vincristine	1.5 mg/m ² d	d1	bolus i.v.
Pirarubicine	40 mg/m ² d	d3	1 hour or bolus i.v.
Cisplatin	20 mg/m ² d	d1-5	120 hours cont. i.v.

Myeloablative chemotherapy

Busilvex	0.8-1.2 mg/m ² per dose every 6 hours up to a total of 16 doses	d -7 to -4	i.v. push or short time
Melphalan	90 mg/m ² d	d -3 to -2	i.v. push or short time

Memorial Sloan Kettering Cancer Center (US) [11]***Induction chemotherapy***Cycle 1,2,4

Cyclophosphamide	2.1 g/m ² d,	d1-2,	6 hours i.v.
Doxorubicine	25 mg/m ² d	d1-3,	72 hours continuous infusion
Vincristine	0.67 mg/m ² d	d1-3,	72 hours continuous infusion

Cycle 3 and 5

Cisplatin	50 mg/m ² d,	d1-4,	1 hour i.v.
Etoposide	200 mg/m ² d,	d1-3,	2 hours i.v.

Myeloablative chemotherapy

none

SIOP Europe Neuroblastoma Group (SIOPEN) [12]***Induction chemotherapy***Rapid COJEC d1-80

Cyclophosphamide	1.050 mg/m ² d	d20,21 and d60,61	push i.v. (+Mesna 1.2g/m ² d)
Vincristine	1.5 mg/m ² d	d0,10,20,30,40,50,60,70,80	push i.v.
Carboplatin	750 mg/m ² d	d0,40	1 hour i.v.
Etoposide	175 mg/m ² d	d0,20,40,60	4 hours i.v.
Cisplatin	80 mg/m ² d	d10,30,50	24 hours i.v.

Myeloablative chemotherapy

Busilvex	0.8-1.2 mg/m ² per dose every 6 hours up to a total of 16 doses	d -7 to -3	i.v. push or short time
Melphalan	140 mg/m ² d	d -2	i.v. push

Supplemental Table S6 Sites of primary tumors by trial (all stages)*

Trial	Patients (N)	Primary tumors (N)	Cervical (%)	Thoracic (%)	Abdominal nonadrenal (%)	Adrenal (%)	Unknown (%)	Other (%)
NB79	188	190	4.7	14.2	24.2	52.6	4.2	0.0
NB82	216	220	5.9	14.5	29.5	47.7	1.8	0.5
NB85	406	415	3.6	15.2	27.2	51.8	2.2	0.0
NB90	933	968	3.1	15.9	28.4	50.4	2.1	0.1
NB97	1200	1238	3.6	16.8	28.2	50.9	0.6	0.0
NB2004	1520	1610	4.0	16.0	30.7	48.4	0.8	0.1
NB79-2004	4463	4641	3.8	16.0	28.9	49.9	1.3	0.1

*178 patients (4.0%) had multiple primary tumors (each counted) or primary tumors at overlapping sites (each counted). Therefore, the number of primary sites exceeds the number of patients by 5.8%.

Supplemental Table S7 Sites of metastases in patients with stage 4 \geq 18 months old by trial

Trial	<i>N</i>	Bone marrow (%)	Bone (%)	OM (%)	Lymph nodes (%)	Liver (%)	Skin (%)	Lung/Pleura (%)	Intra-cranial (%)	Other (%)
NB79	73	83.6	72.6	94.5	20.5	24.7	1.4	2.7	4.1	1.4
NB82	70	75.7	71.4	94.3	15.7	14.3	1.4	0.0	7.1	0.0
NB85	129	88.4	60.5	91.5	25.6	11.6	0.8	0.8	8.5	0.0
NB90	294	86.7	63.3	93.2	19.4	16.7	0.3	4.8	6.8	1.4
NB97	281	91.5	72.6	97.5	21.4	10.0	0.0	5.0	6.8	1.1
NB2004	428	93.0	59.8	96.0	20.6	10.5	0.2	6.5	5.1	4.0
NB79-2004	1275	89.3	64.9	95.1	20.7	12.9	0.4	4.6	6.3	2.0
<i>P</i> value		< 0.001	0.086	0.070	0.951	0.002	n.s.	0.003	0.537	n.s.

N number of patients, n.s. not significant, OM osteomedullary metastases (=bone marrow and/or bone).

Supplemental Table S8 Proportions of 5, 10, 15 and 20-year event-free survival of neuroblastoma subgroups

Trial/ <i>MYCN</i>	Stage/age	<i>N</i>	5-year EFS %	10-year EFS %	15-year EFS %	20-year EFS %
NB79-NB2004	All stages	4463	59±1	57±1	56±1	53±1
NB79		188	44±4	44±4	43±4	39±4
NB82		216	49±3	48±3	48±3	45±4
NB85		406	53±2	51±3	50±3	47±3
NB90		933	59±2	58±2	56±2	55±2
NB97		1200	65±1	63±1	62±1	62±1
NB2004		1520	58±2	55±2	55±2	N.A.
NB79-NB2004	Stages 1-3	2290	78±1	76±1	76±1	73±1
NB79		80	82±5	80±5	80±5	76±6
NB82		102	75±4	74±4	74±4	71±5
NB85		198	78±3	76±3	76±3	71±4
NB90		450	82±2	81±2	81±2	79±2
NB97		695	79±2	77±2	76±2	76±2
NB2004		765	73±2	71±2	71±3	N.A.
NB79-NB2004	Stage 4S	482	73±2	72±2	72±2	72±2
NB79		20	70±10	70±10	70±10	70±10
NB82		21	67±10	67±10	67±10	67±10
NB85		37	78±7	72±7	72±7	72±7
NB90		94	73±5	73±5	73±5	73±5
NB97		119	75±4	75±4	75±4	75±4
NB2004		191	73±4	71±4	71±4	N.A.
NB79-NB2004	Stage 4 ≥18m	1276	24±1	22±1	19±1	18±1
NB79		73	3±2	3±2	0	0
NB82		70	13±4	11±4	11±4	11±4
NB85		129	14±3	11±3	10±3	8±3
NB90		294	25±3	22±2	19±2	18±2

Trial/ <i>MYCN</i>	Stage/age	<i>N</i>	5-year EFS %	10-year EFS %	15-year EFS %	20-year EFS %
NB97		281	32±3	29±3	27±3	27±3
NB2004		429	28±3	24±3	24±3	N.A.
MNA NB90-2004	All	587	33±2	29±2	29±2	29±2
	Stage 1	14	54±14	40±16	40±16	N.A.
	Stage 2	30	51±10	51±10	51±10	N.A.
	Stage 3	100	51±5	43±5	43±5	43±5
	Stage 4 <18m	118	29±4	29±4	29±4	29±4
	Stage 4S	39	41±8	41±8	41±8	41±8
	Stages 1,2,3,4S, stage 4 <18m	301	41±3	37±3	37±3	37±3
	Stage 4 ≥18m	285	24±3	21±3	21±3	21±3
No MNA NB90-2004	All	2664	67±1	65±1	63±1	62±1
	Stage 1	636	91±1	91±1	90±1	90±1
	Stage 2	462	75±2	73±2	72±2	72±2
	Stage 3	456	67±2	64±2	64±2	64±2
	Stage 4 <18m	178	73±3	72±3	67±4	67±4
	Stage 4S	309	77±3	76±3	76±3	76±3
	Stages 1,2,3,4S, stage 4 <18m	2041	78±1	77±1	76±1	76±1
	Stage 4 ≥18m	623	31±2	27±2	23±2	21±2

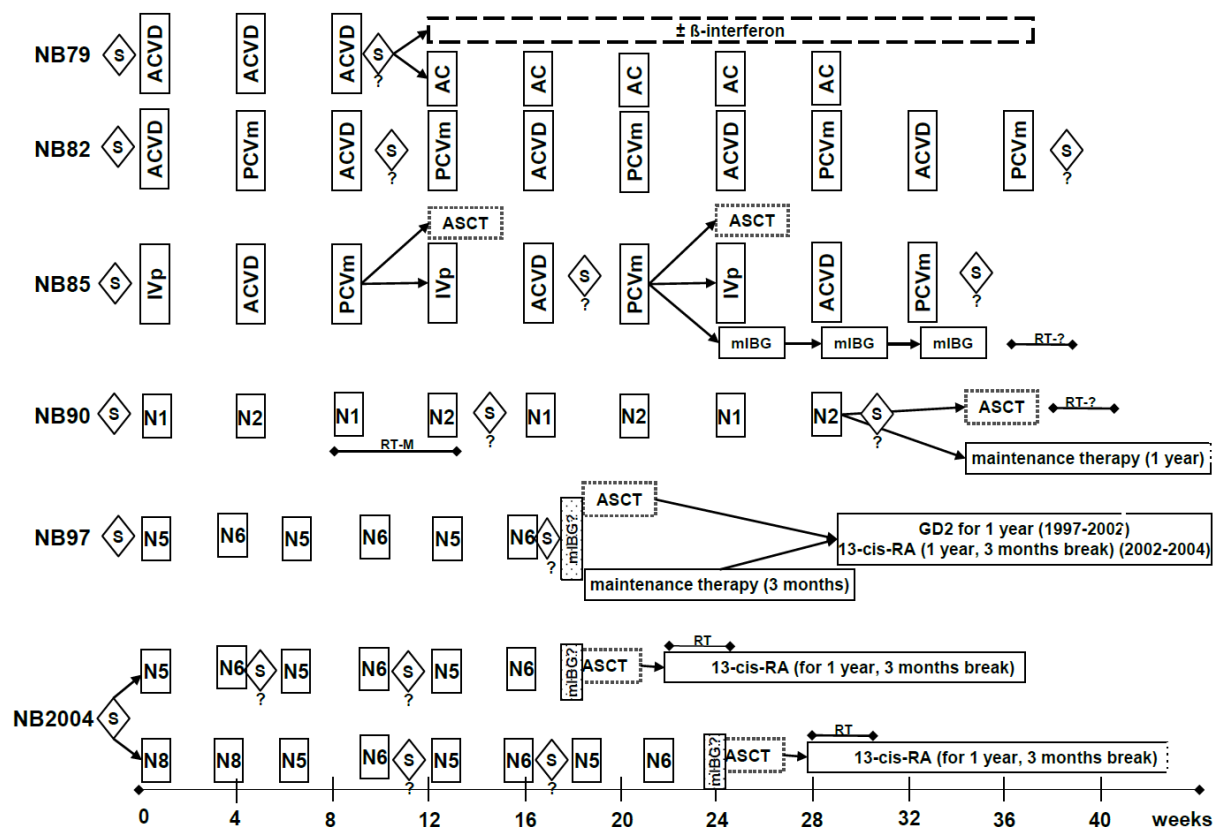
m months, MNA *MYCN* amplification, *N* number of patients, N.A. not applicable

Supplemental Table S9 Proportions of 5, 10, 15 and 20-year overall survival of neuroblastoma subgroups

Trial/ <i>MYCN</i>	Stage/age	<i>N</i>	5-year OS %	10-year OS %	15-year OS %	20-year OS %
NB79-NB2004	All stages	4463	70±1	67±1	66±1	63±1
NB79		188	47±4	46±4	46±4	41±4
NB82		216	56±3	53±3	53±4	52±4
NB85		406	58±3	56±2	55±3	53±3
NB90		933	66±2	63±2	61±2	59±2
NB97		1200	79±1	75±1	74±1	71±2
2004		1520	76±1	72±1	70±2	N.A.
NB79-NB2004	Stages 1-3	2290	90±1	89±1	88±1	86±1
NB79		80	84±4	83±4	83±4	80±4
NB82		102	81±4	80±4	80±4	77±4
NB85		198	84±3	83±3	82±3	81±3
NB90		450	89±2	87±2	86±2	86±2
NB97		695	93±1	92±1	92±1	89±1
NB2004		765	93±1	91±1	91±1	N.A.
NB79-NB2004	Stage 4S	482	84±2	82±2	82±2	78±2
NB79		20	80±9	80±9	80±9	71±9
NB82		21	76±9	71±10	71±10	71±10
NB85		37	86±6	86±6	86±6	78±10
NB90		94	81±4	79±4	79±4	79±4
NB97		119	88±3	84±3	84±3	84±3
NB2004		191	85±3	85±3	85±3	N.A.
NB79-NB2004	Stage 4 ≥18m	1276	35±1	28±1	25±1	23±1
NB79		73	04±2	2±2	0	0
NB82		70	22±5	17±5	17±5	17±5
NB85		129	16±3	12±3	11±3	11±3
NB90		294	31±3	26±3	23±3	20±3

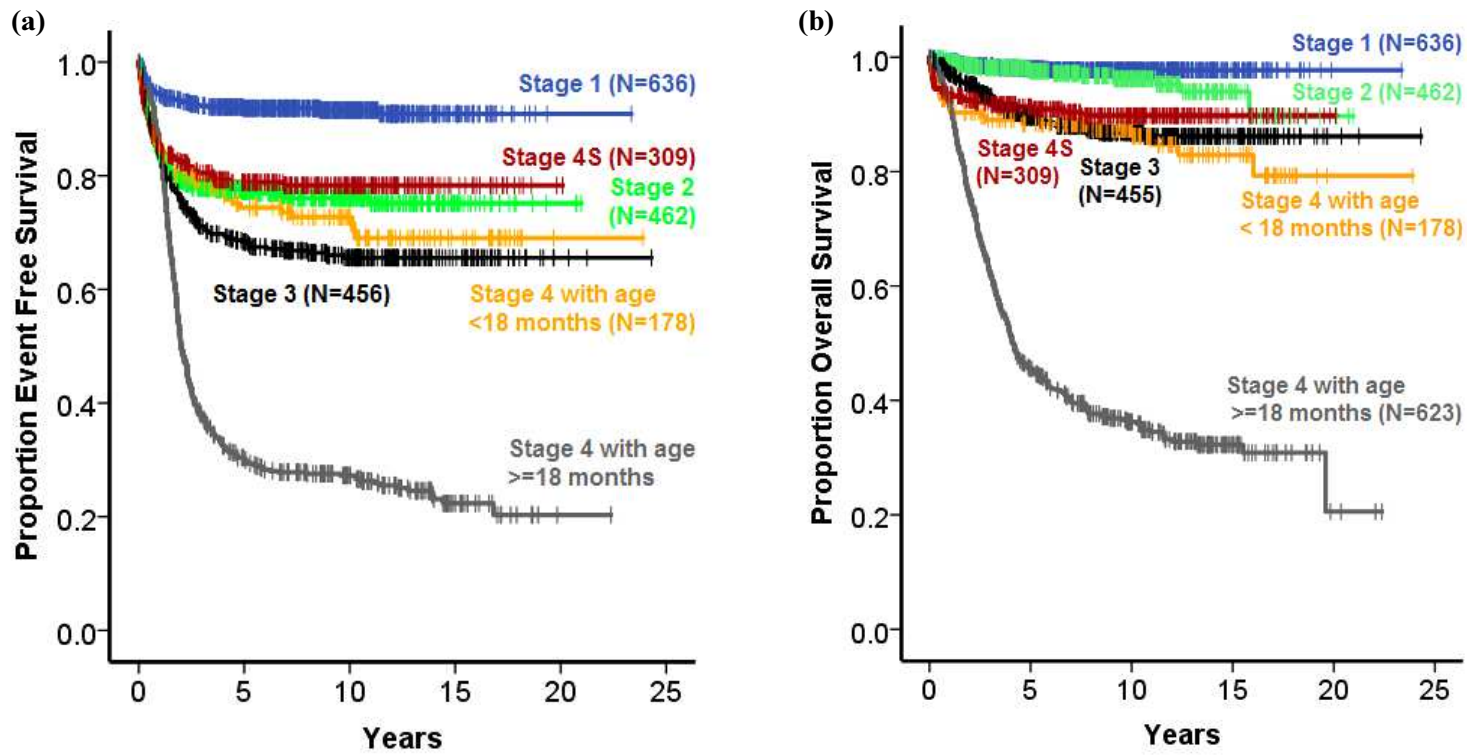
Trial/ <i>MYCN</i>	Stage/age	<i>N</i>	5-year OS %	10-year OS %	15-year OS %	20-year OS %
NB97		281	44±3	33±3	31±3	31±3
NB2004		429	47±3	38±3	33±3	N.A.
MNA NB90-NB2004	All	587	41±2	38±2	36±2	36±2
	Stage 1	14	92±7	92±7	69±21	69±21
	Stage 2	30	57±10	57±10	57±10	N.A.
	Stage 3	100	56±5	54±5	51±5	51±6
	Stage 4 <18m	118	37±5	37±5	37±5	37±5
	Stage 4S	39	45±8	41±9	41±9	41±9
	Stages 1,2,3,4S, stage 4 <18m	301	49±3	48±3	45±3	45±4
	Stage 4 ≥18m	285	34±3	26±3	26±3	26±3
No MNA NB90-NB2004	All	2664	82±1	78±1	76±1	72±1
	Stage 1	636	98±1	91±1	90±1	90±1
	Stage 2	462	97±1	96±1	94±1	88±1
	Stage 3	456	89±2	86±2	86±2	86±2
	Stage 4 <18m	178	88±3	87±3	82±3	76±6
	Stage 4S	309	90±2	89±2	89±2	89±2
	Stages 1,2,3,4S Stage 4 <18m	2041	94±1	94±1	92±1	91±1
	Stage 4 ≥18m	623	47±2	37±2	32±2	26±4

m months, MNA *MYCN* amplification, *N* number of patients, N.A. not applicable



Supplemental Fig. S1 Schematic overview of the treatment elements for high-risk neuroblastoma therapy for the trials NB79-NB2004. For details, see Supplemental Tables S1-S4. Abbreviations:

- AC chemotherapy cycle (doxorubicine,cyclophosphamide)
- ACVD chemotherapy cycle (doxorubicine,cyclophosphamide, vincristine, dacarbazine)
- ASCT autologous stem cell transplantation (different myeloablative regimens)
- C chemotherapy cycle (cyclophosphamide)
- 13-cis-RA 13-cis-retinoic acid (isotretinoin)
- GD2 antibody therapy using antiGd2 antibody
- IVp chemotherapy cycle (ifosfamide, etoposide)
- mIBG ? irradiation using metaiodinebenzylguanidine (if indicated)
- N1 chemotherapy cycle (cisplatinum, etoposide, vindesine)
- N2 chemotherapy cycle (vincristine, dacarbazine, ifosfamide, doxorubicine)
- N5 chemotherapy cycle (cisplatinum, etoposide, vindesine)
- N6 chemotherapy cycle (vincristine, dacarbazine, ifosfamide, doxorubicine)
- N7 chemotherapy cycle (cyclophosphamide)
- N8 chemotherapy cycle (topotecan, cyclophosphamide, etoposide)
- PCV/m chemotherapy cycle (cisplatinum, cyclophosphamide, vepeside)
- RT ? radiotherapy of the primary tumor (external beam irradiation, if indicated)
- RT-M ? radiotherapy of metastases (external beam irradiation, if indicated)
- S surgery
- S? second look surgery (if indicated)



Supplemental Fig. S2 Survival of 2664 patients with non-amplified *MYCN* neuroblastoma by stage and age. Trials NB90, NB97, NB2004. **a** Event-free survival. **b** Overall survival